CORRESPONDENCE

Re: Assessing the Probability That a Positive Report is False: An Approach for Molecular Epidemiology Studies

I read with great interest the very comprehensible commentary by Wacholder et al. *(1)* and share the authors' interpretation of statistical significance. However, I cannot duplicate their calculation leading to their figure 5, in which higher statistical power is associated with a higher false-positive report probability (FPRP). It is my understanding that higher statistical power results in a lower FPRP. I therefore assume that something is wrong in that figure.

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REFERENCE

(1) Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 2004;96:434–42.

NOTE

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RESPONSE

Dr. Dubben notes that a study with higher statistical power will have a lower false-positive report probability (FPRP) than a study with lower statistical power, as seen in equation 1 and in figures 1 and 2 of our original paper *(1)*. He is puzzled, however, by figure 5 *(1)*, which shows FPRP increasing with increasing statistical power.

Our paper's figure 5 *(1)* shows the reduction in statistical power with fixed sample size from demanding stronger evidence for calling a study positive, whether by an FPRP or *P*-value criterion. By contrast, sample size is not fixed in figures 1, 2, and 3 *(1)*, which show the influence of prior probability and of statistical power, manifested through sample size, on FPRP. When sample size is fixed, there is an additional constraint implicit in equation 2 because varying α has a direct effect on statistical power. On the other hand, all the variables on the right side of equation 1 are free to vary independently when sample size is not fixed.

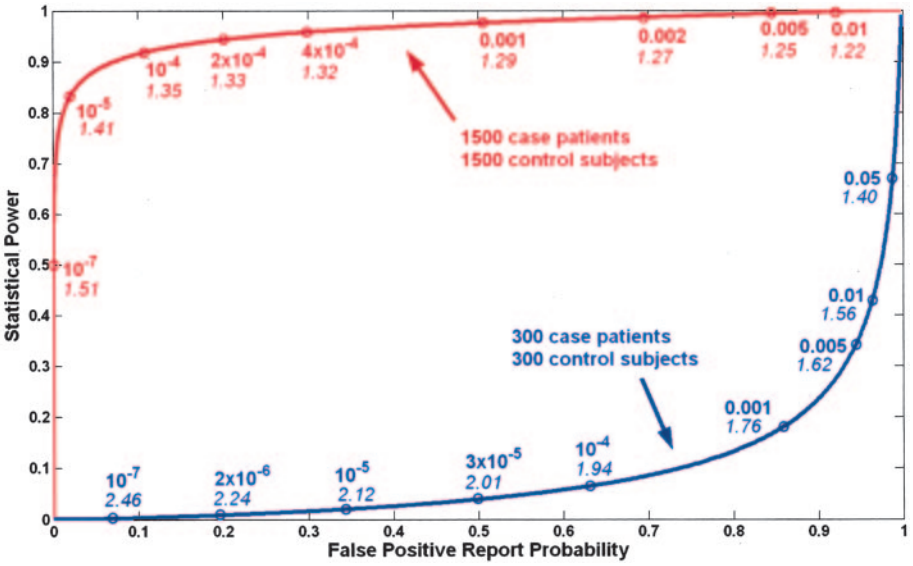

Fig. 1. Effect of decreasing the false-positive report probability (FPRP) criterion for a noteworthy finding on α level, the minimum observed odds ratio that will achieve the FPRP criterion, and statistical power. This figure is a reprise of figure 5 in our original publication *(1)* with added display of selected α levels (in boldface) and the odds ratio estimates (in italics) that generate the given FPRP value or *P* value and power. The graphs show how changing the FPRP criterion changes the statistical size (α), the odds ratio estimates that will achieve the FPRP criterion and the statistical power to detect an odds ratio of 1.5, when prior probability is 0.001 and allele frequency (*q*) is 0.3 for 300 (blue) or 1500 (red) case patients and control subjects. Note that small increases in the observed odds ratio can greatly reduce the FPRP value and *P* value in studies with 1500 case patients and 1500 control subjects.

Figure 1 in this response shows the same curves from the original paper's figure 5 *(1)* labeled to indicate the *P* value (in boldface) and the odds ratio (in italics) that corresponds to the *P* value that would give the FPRP value on the *x*-axis and statistical power on the *y*-axis. For example, the figure shows that the greater stringency from imposing an FPRP criterion of 0.2 instead of 0.5 in a study with 1500 case patients and 1500 control subjects does not substantially reduce statistical power for detecting an odds ratio of 1.5 when the prior probability is 0.001 and the allele frequency among the control subjects is 0.3. Under the more stringent criterion, associations with *P* values below about 0.00023 instead of below 0.0010, or, equivalently an observed odds ratio below 1.33 instead of below 1.29 if the observed allele frequency among controls was 0.3, would be deemed noteworthy for an FPRP of 0.2, based on equation 1 of our original paper *(1)*. In fact, regardless of the preset FPRP criterion, we would report an FPRP value of 0.2 if the observed *P* value were 0.00023. Although the editorial by Thomas and Clayton called FPRP calculations from *P* values "inappropriate," we argue that the FPRP value can be interpreted as the lowest FPRP for which the finding meets a preset criterion for noteworthiness, just as the observed *P* value is the lowest α level for which the finding meets the criterion for statistical significance *(1)*.

We believe that our approach provides both results and conclusions broadly similar to those from more complicated methods, as noted by Thomas and Clayton *(2)*, with the advantage that it can be implemented and understood by a large fraction of the cancer research community. We look forward to further discussions of our work *(2,3,4)* and related ideas *(5)* as we study steadily increasing numbers of genes with steadily decreasing prior probabilities in molecular epidemiology studies.

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REFERENCES

(1) Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 2004;96:434–42.
(2) Thomas DC, Clayton DG. Betting odds and genetic associations. J Natl Cancer Inst 2004; 96:421–3.
(3) Sellers TA. Genetic ancestry and molecular epidemiology. Cancer Epidemiol Biomarkers Prev 2004;13:499–500.
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(5) Colhoun HM, McKeigue PM, Davey Smith G. Problems of reporting genetic associations with complex outcomes. Lancet 2003;361:865–72.

NOTES

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